

REMARKS

Claim 1 has been amended identically as in the Amendment Under 37 C.F.R. § 1.116 filed on December 27, 2002. Claim 2 has been deleted without prejudice and rewritten in independent form as claim 64. Claims 4 and 8 have been previously allowed. New claims 38-63 find support in the original claims. In addition, support for claim 38 is found on page 4, lines 9-23 of the present application. Claim 52 merely combines the limitations of claims 1 and 3 but eliminates alcohol and carbohydrate from the list of chemically defined components.

In the Advisory Action, the Office has not appeared to maintain the rejection under 35 U.S.C. §112, second paragraph that was made in the final Office action, so it is assumed that this rejection has been withdrawn.

Summary of the invention

The invention resides in the description of a process for utilizing a defined medium for production of antibiotics on an industrial scale. Please see page 4, lines 1-9 of the present specification. As is set forth in the specification, chemically defined media have been used in laboratory procedures in the past, but the problems presented by industrial scale fermentations are so different that it is not possible to extrapolate practices in the laboratory to the industrial environment. Please see page 2, line 27 through page 3 line 24. Chemically defined media, used in the present industrial scale process, differ from complex or natural media conventionally used in industrial scale processes, in that chemically defined media use pure compounds in precisely defined proportions whereas complex or natural media are not completely defined. A further discussion of this distinction is found on page 5, last paragraph of the Amendment mailed December 27, 2002.

Issue

The outstanding issue is whether *prima facie* obviousness under 35 U.S.C. §103 over Hogye, *et al.*, Derwent Abstract 1987-357537 (Hogye) in view of U.S. Patent 5,731,165 issued to Bovenberg, *et al.* (Bovenberg) and *Microbiology*, fourth edition, Pelczar, Reid and Chan pages 853-856 (*Microbiology*) has been established where a) none of the individual references teaches the use of a chemically defined medium in a 10 m³ volume scale process as defined specifically in the claims, b) where no motivation to combine the documents is set forth by the Office, and c) where there is no expectation that a combination, if made, would arrive at a process that would be successful on an industrial scale.

A. Each of Cited References Do Not Disclose or Suggest Defined Industrial Process Using Claimed Medium Containing Only Chemically Defined Components

On page 4, lines 1-4 of the Office action mailed August 27, 2002, the Office alleges that *Microbiology*:

teaches that penicillin was the first antibiotic to be produced industrially utilizing *a similar standard chemically defined medium* as the claimed invention's chemically defined medium (see, especially, e.g., page 855-856, the steps) (emphasis added).

The Office further alleges on page 4, lines 5-10 of the Office action mailed August 27, 2002, that *Microbiology*:

teaches it is common to add other chemicals (i.e. carbon and nitrogen sources) to a chemically defined medium for the production [of] the Beta-Lactam... (see e.g., page 855, step 5, states the additions [sic] of chemicals to the medium serves as precursors for synthesis of penicillin (emphasis in original).

It is respectfully submitted that the Office has mischaracterized the teachings of *Microbiology*. As an initial matter, a chemically defined medium is nowhere disclosed in *Microbiology*. Moreover, Step 5 on page 855 of *Microbiology* to which the Office refers states:

"The addition of chemicals to the medium *which serve as precursors for the synthesis of penicillin* (emphasis added) ① It is respectfully submitted that these "chemicals" are not "similar" to the sole carbon or nitrogen sources as defined, for example, in claim 1 but rather refer to complex raw materials. To clarify, the precursors to which Step 5 refers is related to the conversion of complex raw material precursors to β -lactam, whereas the claimed invention defines an industrial process for *de novo* production of β -lactam.

There is no other disclosure in *Microbiology* that refers to chemically defined media. In fact, Figure 40-4 on page 856 of *Microbiology* refers to the manufacture of penicillin using "corn-steep liquor" which is a very complex raw material which precludes this medium from being chemically defined as claimed.

Moreover, neither Hogue nor Bovenberg are relevant. ① Hogue is silent on the volume of the culture. The Office appears to agree with this assertion as the anticipation rejection based on this reference made in the Office action mailed December 18, 2001 was withdrawn based on applicants' argument that Hogue does not disclose a process on an industrial scale having the minimum volume of 10 m^3 as claimed. In pointing to the abstract, the Office alleges that the process uses "a fermentation medium consisting of chemically defined constituents of a nitrogen source such as ammonium sulphate and an ammonium hydroxide," however, it is not clear from this Abstract that ammonium sulfate and ammonium hydroxide are actually the sole sources of nitrogen, as they are disclosed for use in controlling pH. Please see the sentence bridging pages 3-4 of the Office action mailed December 18, 2001.

In addition, Bovenberg discloses only small scale production of phenylacetyl-7-ADCA, as illustrated by Example 1 therein which has a fermentation volume of 15 ml. Please see Bovenberg, column 5, line 43. Further, Bovenberg does not describe a chemically defined

medium but rather uses phenylacetic acid as a precursor to make phenylacetyl-7-ADCA in a medium comprising cotton seed meal and corn steep solids in an amount greater than 10%. As neither reference defines the fermentation volume as claimed, neither can suggest the claimed invention that is directed to using a chemically defined medium in an industrial scale process.

Moreover, none of the references mentions the volume scale as claimed of at least 10 m³ as claimed. As the Office has not pointed to such disclosure or suggestion, *prima facie* obviousness has not been established.

Even if, for the sake of argument, the Office had pointed to a disclosure in the references of such volume scale, as the individual references do not alone describe or suggest the invention, there must be motivation to combine the references in order to establish *prima facie* obviousness. Please see MPEP § 2143.

B. No Motivation to Combine References

The Office has not addressed the applicants' arguments made in response to the final Office action with regard to a lack of motivation to combine the references. In the Advisory Action, the Office merely alleges "Hogye et al. teach the production of penicillin utilizing only chemically defined components and Microbiology teach it is well known in the art to produce penicillin on an industrial scale and/or of mass production" but provides no motivation to combine the disclosures. It is well settled that there must motivation to combine the elements in one reference with another to arrive at the claimed invention without the benefit of using applicants' disclosure. Applicants respectfully request the Office to clearly set forth the motivation upon which it relies to fulfill this element in establishing *prima facie* obviousness in accordance with MPEP §2143 and US patent practice. Otherwise it is respectfully submitted that there is no motivation to combine Hogye's process, which apparently does not contemplate an

industrial process, with *Microbiology's* industrial process or Bovenberg's small scale production process to arrive at the claimed invention without the benefit of impermissible hindsight.

C. No Expectation that Hogye's Process in Combination with the Disclosures of Bovenberg and *Microbiology* Will Result in Successful Industrial Scale Production as Claimed

The present application points out, for example, on page 3, lines 8-18, that defined media to produce materials on a laboratory scale is well known. The problem arises when defined media are to be used *industrially*. The Office does not point to a reasonable expectation in the cited references or otherwise that shows that this problem may be overcome on an industrial scale as addressed by the present claims. Therefore, it is respectfully submitted that yet another element required to establish *prima facie* obviousness, namely, a reasonable expectation that a modification of the references would be successful, has not been established.

D. Mutated Strain as Claimed Not Defined in References

New claims 38-51 are similar to claim 1 and those claims dependent thereon, however, these new claims are directed to a microbial strain that is mutated or is a recombinant β -lactam producing strain that is capable of being fermented on said volume scale and that has been selected for improved performance on the chemically defined medium and/or increased β -lactam production in comparison to a parent strain. None of the references disclose such a mutated or recombinant strain. As such, these claims further distinguish over the cited references.

E. Chemically Defined Components as Defined in Claims 52-63 Not Disclosed in Cited References

Claims 52-63 are similar to claim 3 but do not include alcohol or an organic acid in the Markush group of chemically defined components. Although the applicants disagree with the

Office's interpretation of what Hogye discloses, these claims now exclude Hogye's critical precursors for Penicillins G and V, thus further distinguishing over the cited references.

For the reasons stated above, it is respectfully submitted that the claims are not obvious over the cited references and withdrawal of this rejection is respectfully requested.

F. Complex Portion of Medium Must be Less than 10%

Regarding new claims 39 and 64 which are similar to claim 2, none of the references teach that the complex portion of the medium must be less than 10% of the total carbon and/or nitrogen sources in the medium. Therefore, these claims also distinguish over the references.

CONCLUSION

The applicants respectfully request the Office specifically address the following when responding to this Preliminary Amendment:

1. Please point to the disclosure in Microbiology of a "similar standard chemically defined medium."
2. Please point to the disclosure of a volume scale of at least 10 m³ in any of the references.
3. Please set forth the particular motivation to combine the use of a chemically defined medium with an industrial scale process.
4. Please indicate where in any of the references is a suggestion that the claimed chemically defined medium will be successful in an industrial scale process.
5. Please point to the disclosure of a medium that contains chemically defined components and complex components that are less than 10% of the total carbon and/or nitrogen sources.

Otherwise, the applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested. If the Examiner is not convinced by the above arguments that the claims are in condition for allowance, a telephonic interview is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 246152012710.

Respectfully submitted,

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By:



Carolyn A. Favorito
Registration No. 39,183

Morrison & Foerster LLP
3811 Valley Centre Drive,
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5195
Facsimile: (858) 720-5125